

# Safety and efficacy of oral transmucosal fentanyl citrate for prehospital pain control on the battlefield

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<b>BACKGROUND:</b>	Acute pain, resulting from trauma and other causes, is a common condition that imposes a need for prehospital analgesia on and off the battlefield. The narcotic most frequently used for prehospital analgesia on the battlefield during the past century has been morphine. Intramuscular morphine has a delayed onset of pain relief that is suboptimal and difficult to titrate. Although intravenously administered morphine can readily provide rapid and effective prehospital analgesia, oral transmucosal fentanyl citrate (OTFC) is a safe alternative that does not require intravenous access. This study evaluates the safety and efficacy of OTFC in the prehospital battlefield environment.
<b>METHODS:</b>	Data collected during combat deployments (Afghanistan and Iraq) from March 15, 2003, to March 31, 2010, were analyzed. Patients were US Army Special Operations Command casualties. Patients receiving OTFC for acute pain were evaluated. Pretreatment and posttreatment pain intensities were quantified by the verbal numeric rating scale (NRS) from 0 to 10. OTFC adverse effects and injuries treated were also evaluated.
<b>RESULTS:</b>	A total of 286 patients were administered OTFC, of whom 197 had NRS pain evaluations conducted before and approximately 15 minutes to 30 minutes following treatment. The difference between NRS pain scores at 0 minutes (NRS, 8.0 [1.4]) and 15 minutes to 30 minutes (NRS, 3.2 [2.1]) was significant ( $p < 0.001$ ). Only 18.3% (36 of 197) of patients were also administered other types of analgesics. Nausea was the most common adverse effect as reported by 12.7% (25 of 197) of patients. The only major adverse effect occurred in the patient who received the largest opioid dose, 3,200- $\mu$ g OTFC and 20-mg morphine. This patient exhibited hypoventilation and saturation of less than 90% requiring low-dose naloxone.
<b>CONCLUSION:</b>	OTFC is a rapid and noninvasive pain management strategy that provides safe and effective analgesia in the prehospital battlefield setting. OTFC has considerable implications for use in civilian prehospital and austere environments. ( <i>J Trauma Acute Care Surg.</i> 2012;73: S490–S495. Copyright © 2012 by Lippincott Williams & Wilkins)
<b>LEVEL OF EVIDENCE:</b>	Therapeutic study, level IV.
<b>KEY WORDS:</b>	Acute pain; prehospital analgesia; battlefield; oral transmucosal fentanyl citrate; pain management.

Validating whether a therapy is practical in the prehospital setting requires using the therapy in that setting.<sup>1,2</sup> Therapies that are effective in the hospital may ultimately prove suboptimal for use in the prehospital setting and vice versa. Throughout history, the US military's strategies for managing pain on the battlefield have largely been shaped by the trials and tribulations of war and conflict as well as by the advancements and availability of pain management technologies.

Attempting to provide adequate analgesia in the prehospital battlefield environment introduces additional challenges invoked by environmental extremes, logistical constraints, evacuation limitations, and other factors imposed by enemy forces. Novel pain management strategies must consider these battlefield realities to be practical and successful when applied in this prehospital setting.

Beecher<sup>3</sup> conducted landmark research during World War II showing that 75% of badly wounded casualties arriving at a field hospital had such nominal pain that they did not want additional pain relief medication, although pain medication was readily available and more than 5 hours had passed since they had last received morphine. However, casualties who reported bad pain were more apt to request medication for pain relief, which demonstrated the importance of addressing both the patient's reported pain and desire for pain medications. Singer et al.<sup>4</sup> recently noted similar findings in a civilian emergency department (ED) patient population.

Recent studies have indicated that a failure to recognize and appropriately treat acute pain on the battlefield may result in an increased incidence of chronic pain syndromes and posttraumatic stress disorder.<sup>5–10</sup> Although most US military providers are aware of the potential long-term consequences of failing to identify and treat acute pain early in the ED and prehospital environments, they most likely undertreat acute pain commensurate to their civilian counterparts.<sup>11–16</sup> Because

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The authors have no relationships, financial or otherwise, that might be perceived as a conflict of interest. This article has been read and approved by all authors and all authors meet criteria for authorship. This article was prepared as part of official government duties. The views, opinions, and findings contained in this report are those of the authors and should not be construed as reflecting the views of the Department of the Army or the Department of Defense unless otherwise stated. This report was approved for public release by the US Army Special Operations Command Operational Security Office and the Public Affairs Office on May 4, 2011.

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DOI: 10.1097/TA.0b013e3182754674

Report Documentation Page				Form Approved OMB No. 0704-0188	
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1. REPORT DATE <b>01 DEC 2015</b>		2. REPORT TYPE <b>N/A</b>		3. DATES COVERED <b>-</b>	
4. TITLE AND SUBTITLE <b>Safety and efficacy of oral transmucosal fentanyl citrate for prehospital pain control on the battlefield</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) <b>Wedmore I. S., Kotwal R. S., McManus J. G., Pennardt A., Talbot T. S., Fowler M., McGhee L.,</b>				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release, distribution unlimited</b>					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>UU</b>	18. NUMBER OF PAGES <b>6</b>	19a. NAME OF RESPONSIBLE PERSON
a REPORT <b>unclassified</b>	b ABSTRACT <b>unclassified</b>	c THIS PAGE <b>unclassified</b>			

of this, there is a renewed interest in the recognition, treatment, education, and research of battlefield pain management.

Acute pain is a complex symptom that requires treatment to prevent adverse sequelae and improve prognoses. Nociceptive stimuli activate multiple neuronal signaling pathways, which result in diverse types of pain that respond differently to various medication strategies, dependent not only on drug choice but also on route of administration. Currently, prehospital medical providers continue to rely heavily on intramuscular (IM) morphine for battlefield pain management despite clinical practice guidelines that recommend otherwise.<sup>5,10</sup> In addition to the delayed onset of action and titration difficulties inherent with IM injection, trauma patients who are hemorrhaging and hypothermic will shunt blood centrally to vital organs and further propagate these difficulties. As peripheral blood flow to muscles is reduced, IM morphine absorption is affected, and medical providers may inject additional IM morphine in an attempt to alleviate pain. As resuscitation efforts successfully restore peripheral blood flow to muscles, IM morphine is released into the circulation. The timing and degree of this delayed release may result in less than favorable outcomes.

Opiate analgesics have historically been the most effective category of pain medications used for severe pain. Morphine sulfate is the classic opioid that has been widely used since its initial isolation and crystallization from opium poppy in the early 1800s. Despite its widespread use, morphine is not exceptionally potent for pain control and can cause significant adverse effects, including hemodynamic instability, immune function suppression, and heart rate and respiration reduction. However, morphine has a long history of use that provides a sense of familiarity and comfort to medical providers. In addition, morphine provided through intravenous (IV) methods can provide rapid and effective analgesia that can be titrated. To improve on morphine's limitations, chemists and pharmacists have synthesized, developed, and manufactured multiple morphine-based derivatives that are more potent than morphine while eliciting fewer adverse effects. One of these preparations is fentanyl.

Fentanyl citrate is a medication approved by the US Food and Drug Administration that is approximately 100 times more potent than morphine with fewer adverse effects. Classified as an opioid, fentanyl is a synthetic agonist of the  $\mu$  receptor that has been used parenterally since the early 1960s. Because fentanyl quickly crosses the blood-brain barrier, allowing for rapid onset of pain relief, it is often used for treatment of acute pain after trauma. A recent study found that after a fentanyl-based pain management protocol was implemented for trauma patients in the ED, there was a marked reduction in time to initial analgesia, an increase in patients achieving analgesia, and no increase in adverse events compared with those who did not receive fentanyl.<sup>17</sup> Fentanyl has also been shown to be safe and effective for out-of-hospital pain management.<sup>18,19</sup>

Oral transmucosal fentanyl citrate (OTFC) is a fentanyl preparation manufactured as a lozenge on a stick that is commonly available as Actiq in six dosage strengths (200, 400, 600, 800, 1,200, and 1,600  $\mu$ g). Absorption through the oral mucosa facilitates rapid analgesic onset, while the remaining medication

that is swallowed assists with the prolonged analgesic effect. This noninvasive, fast-acting, and long-lasting preparation of fentanyl is ideally suited for use as an analgesic to treat acute pain in the prehospital component of the battlefield.<sup>6,20</sup>

This study analyzes the use of OTFC in the prehospital battlefield environment by medical providers assigned to the US Army Special Operations Command. Characterized is the medication's safety and effectiveness. Also reported are injuries treated and adverse effects encountered.

## PATIENTS AND METHODS

Patients presenting to a medical provider in the prehospital battlefield environment were treated in accordance with protocols and clinical practice guidelines established by unit physicians within the US Army Special Operations Command. Medical providers depicted in this study were previously trained above the emergency medical technician-paramedic level and included Special Operations combat medics, Special Forces medical sergeants, physician assistants, and physicians. Treatment regimens, to include management of acute pain, were documented by prehospital medical providers and further captured by prehospital registries maintained by unit physicians.

Patients presenting with acute pain were asked to verbally rate their pain on a numeric rating scale (NRS) from 0 to 10, with 0 representing no pain and 10 representing the most severe pain. Patients were then provided analgesics by prehospital medical providers as deemed appropriate for pain relief, the injury, and the clinical setting. Those patients who received OTFC, or Actiq, were included for evaluation in this study.

Patients were evaluated and monitored by medical personnel before, during, and on a continuous basis after administration of OTFC as per established protocols. In addition to observation and vital signs monitoring, frequent pulse oximetry testing was also conducted. Approximately 15 minutes to 30 minutes after OTFC administration, patients were again asked to rate their pain on the NRS scale. To ensure complete capture of events, data from casualty cards, medical records, and medical logs were cross-referenced with treating providers upon return to the United States. Every attempt to collect all data points was made. Individuals with missing data points were included and assimilated appropriately, with no data entered for missing data points. Thus, averages were not affected by missing data points.

Statistical analyses of medians, means, SDs, and confidence intervals were accomplished using SPSS PASW Statistics 18. Hypothesis testing was conducted using (1) the Wilcoxon signed-rank test for pairwise comparison of pre- and post-OTFC NRS scores; (2) the Mann-Whitney U-test for analysis of adverse effects, dosage, and reduction in NRS scores; (3) the Student's *t* test for the difference between mean pre- and post-OTFC NRS scores; (4) a one-way analysis of variance for the difference in means between patients, those with and those without adverse effects, for both dosage and NRS scores; and (5) the Spearman correlation test to determine relationships among OTFC dosage, pain scores, and adverse effects. Statistical significance was set at  $p < 0.05$ .

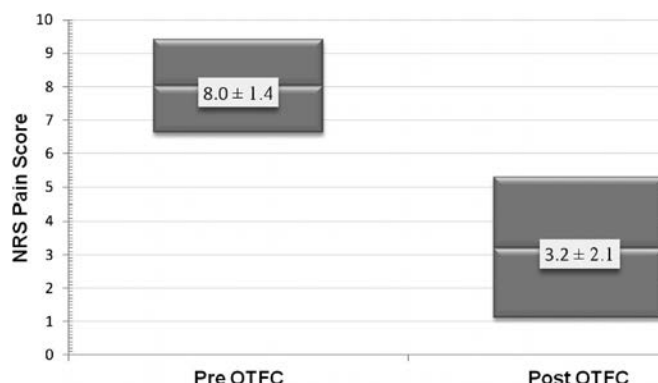
The institutional review board at Brooke Army Medical Center, Fort Sam Houston, Texas, provided approval to conduct this study.

## RESULTS

Data were collected on 286 patients who received OTFC in the prehospital battlefield environment in Afghanistan and Iraq from March 15, 2003, to March 31, 2010. Of these patients, 197 casualties had written documentation of NRS pain evaluations conducted before and 15 minutes to 30 minutes after treatment. Patient ages ranged from 8 years to 55 years, with the majority between 20 years and 40 years, which is reflective of the age of most personnel in the military. The NRS study population included 6.6% (13 of 197) females and 93.4% (184 of 197) males. Most patients, 79.2% (156 of 197), received OTFC for pain management of traumatic extremity injuries. Patients receiving OTFC had various mechanisms of injury, but gunshot wounds (GSWs) were the most prevalent at 37.6% (74 of 197), followed by orthopedic injuries not caused by blast or GSWs at 37.6% (74 of 197), lacerations and shrapnel wounds at 18.3% (36 of 197), partial or complete amputations at 3.6% (7 of 197), and burns at 2% (4 of 197). Many in these last three groups were caused by blasts. In some cases, a combination of injury mechanisms was present. Various other causes of acute pain were noted in the remainder of patients treated with OTFC, including dog bites, kidney stones, root canals, and scorpion stings.

The Wilcoxon signed-rank test for pairwise comparison of pre- and post-OTFC NRS scores was found to be significant ( $p < 0.001$ ). Almost all patients, 97.0% (191 of 197), reported lower pain scores following OTFC administration. The difference in mean NRS pain scores between evaluations conducted at 0 minutes (NRS, 8.0 [1.4]) and 15 minutes to 30 minutes (NRS, 3.2 [2.1]) was also found to be significant ( $t$  test,  $p < 0.001$ ) (Fig. 1). Only 6 patients did not report experiencing less pain. The mean (SD) dose of OTFC used was 962.4 (452.7)  $\mu\text{g}$ , with 1 patient receiving 3,200  $\mu\text{g}$ , 1 patient receiving 2,400  $\mu\text{g}$ , 48 receiving 1,600  $\mu\text{g}$ , 3 receiving 1,200  $\mu\text{g}$ , 114 receiving 800  $\mu\text{g}$ , 28 receiving 400  $\mu\text{g}$ , and 2 receiving 200  $\mu\text{g}$ . In 84.8% (167 of 197) of cases, 800  $\mu\text{g}$  of OTFC or greater was used. Only 18.3% (36 of 197) of patients required other types of analgesics to ultimately control their pain, with 81% (29 of 36) of these patients receiving additional opioids, primarily morphine. Antiemetic drugs were administered to 10.2% (20 of 197) of patients, with 60% of these patients receiving ondansetron and 40% of these patients receiving promethazine. Records do not indicate whether antiemetic drugs were provided as a prophylactic or for actual treatment of nausea.

The most commonly reported minor adverse effect was nausea (12.7%, 25 of 197), followed by pruritis (4.1%, 8 of 197), drowsiness (1.0%, 2 of 197), and dizziness (0.5%, 1 of 197). A major adverse event was reported in one patient who experienced hypoventilation after receiving 3,200  $\mu\text{g}$  of OTFC and 20 mg of morphine sulfate intravenously administered for a total disruption and dislocation of the knee. Although finger pulse oximetry recorded an oxygen saturation of 88% to 90%,



**Figure 1.** Mean NRS pain scores, pre- and post-OTFC administration, for patients ( $n = 197$ ) treated in the prehospital battlefield environment. The difference in mean NRS pain scores between evaluations conducted at 0 minutes (NRS, 8.0 [1.4]) and 15 minutes to 30 minutes (NRS, 3.2 [2.1]) was found to be significant ( $p < 0.0001$ ).

this patient responded readily to stimulation, 2 L to 4 L of oxygen administered by nasal cannula, and low-dose naloxone. This case, previously reported in the literature,<sup>6</sup> occurred in March 2003 when OTFC was first used on the battlefield. No other major adverse event has been reported since that case.

Although NRS scores were not captured for 89 patients, 18 had adverse event data collected with no adverse events noted. While it could not be determined whether any minor adverse events such as nausea or pruritis were recorded in the remaining 71 patients, all were active duty military members who remained within the military medical system and neither were completely lost to follow-up nor were major adverse events recorded at any later time. Thus, the observed rate of major adverse events was 3.5 per 1,000 patients treated.

The Mann-Whitney U-test indicated that when compared with patients who did not have adverse effects, patients with adverse effects received different doses of OTFC ( $p = 0.008$ ), reported different pain scores before receiving OTFC ( $p = 0.017$ ), and exhibited different magnitudes of pain relief as evidenced by the mean difference in pain scores before and after OTFC ( $p = 0.026$ ). However, the means of the pain scores reported after OTFC administration were no different between these two groups ( $p = 0.949$ ).

Descriptive statistics and one-way analysis of variance tests showed that patients who experienced adverse effects had reported greater pain before treatment (8.5 [1.3] vs. 7.9 [1.4],  $p = 0.015$ ). Patients who reported adverse effects also received higher doses of fentanyl (1,167 [561]  $\mu\text{g}$  vs. 917 [413]  $\mu\text{g}$ ,  $p = 0.003$ ). Spearman's rank correlation coefficient also revealed positive correlations between dose and presence of adverse effects ( $p = 0.178$ ), as well as between the presence of adverse effects and the difference between the two pain scores ( $p = 0.160$ ,  $p < 0.05$ ).

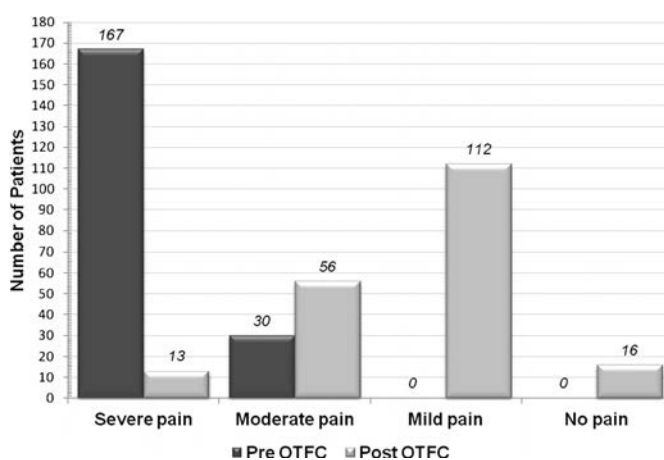
Using the NRS classification of 0 = no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain, and 7 to 10 = severe pain, all patients who received OTFC reported moderate pain (15.2%, 30 of 197) or severe pain (84.8%, 167 of 197) before OTFC administration. This is consistent with unit clinical

practice guidelines recommending the use of OTFC for treatment of patients who reported pain at these levels. At 15 minutes to 30 minutes following OTFC administration, 8.1% (16 of 197) of patients reported no pain, 56.9% (112 of 197) reported mild pain, 28.4% (56 of 197) reported moderate pain, and 6.6% (13 of 197) reported severe pain (Fig. 2).

## DISCUSSION

During the past three decades, numerous studies in multiple countries have documented the use, safety, and effectiveness of OTFC as administered to treat acute and chronic pain in both children and adults.<sup>21–44</sup> OTFC use has been documented for opiate-dependent breakthrough pain in patients with cancer, procedural and perioperative pain control, and pain management in the ED.<sup>21–44</sup> OTFC use has also been previously documented for prehospital treatment of acute pain on the battlefield.<sup>6</sup>

While fentanyl is 100 times more potent than morphine, it does still function through the  $\mu$  opioid receptor and thus has the potential to cause similar major and minor adverse effects that would prove suboptimal if exhibited in the prehospital battlefield environment. Major adverse events can include respiratory depression, chest wall rigidity, and bradycardia. Although only one major adverse event was reported in this study, providers should remain cognizant of the major adverse effects of fentanyl, especially when administered at higher doses and in combination with other medications. Minor adverse effects of fentanyl can include nausea, pruritis, emesis, lightheadedness, and transient oxygen desaturation.



**Figure 2.** NRS pain classification, pre- and post-OTFC administration, for patients (n = 197) treated in the prehospital battlefield environment. NRS pain classification (0 = no pain, 1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain). All patients reported moderate (15.2%, 30 of 197) or severe pain (84.8%, 167 of 197) before OTFC administration. At 15 minutes to 30 minutes after OTFC administration, 8.1% (16 of 197) of patients reported no pain, 56.9% (112 of 197) reported mild pain, 28.4% (56 of 197) reported moderate pain, and 6.6% (13 of 197) reported severe pain.

The most common minor adverse effect in this study was nausea as reported in 12.7% of cases. This finding is consistent with OTFC adverse effects commonly reported in the literature.<sup>6,21–44</sup>

Because OTFC use does not require IV access, this non-invasive route of analgesic administration saves valuable time, is easier to perform during nighttime operations, and is preferable for providers who do not otherwise need to initiate an IV in the combat setting. This is especially beneficial when considering current clinical practice guidelines that recommend forgoing intravenously administered fluids for prehospital battlefield resuscitation of hemodynamically stable patients.<sup>10</sup>

If injuries dictate resuscitation requiring IV access, then intravenously administered analgesic options should be considered given that access has already been established. In the prehospital battlefield environment, intravenous resources and the time dedicated toward such efforts are best reserved for hemodynamically unstable patients who require IV resuscitation to sustain life. Because the noninvasive characteristic of OTFC is of benefit for the prehospital battlefield environment, other noninvasive fentanyl preparations such as buccal tablets, nebulizers, intranasal spray, and buccal soluble film may also have application in this setting and should be further explored.<sup>45–48</sup>

This study supports the use of OTFC in the prehospital battlefield environment and demonstrates that it possesses both safety and efficacy. It also suggests that it is being administered correctly. As one would expect, patients reporting greater pain were given higher doses of OTFC. This, in turn, likely resulted in the increased adverse effects. However, OTFC was also successful in providing sufficient analgesia to these patients because there was no difference in the post-OTFC pain scores for patients that reported adverse effects from those who did not report adverse effects, although the former had higher initial pain scores.

All patients depicted in this study received OTFC for acute pain. Combat injuries resulting from blunt and penetrating trauma accounted for most patients, with most receiving OTFC for pain management of traumatic injuries of the extremities. Although GSWs were the most prevalent mechanism of injury, blast, burn, and other orthopedic and soft tissue injuries accounted for most of the remaining injuries. Most patients (84.8%) in this study received at least 800  $\mu$ g of OTFC. This study also depicted safety and efficacy of this 800  $\mu$ g dose for acute pain. Thus, an initial dose of 800  $\mu$ g is recommended for the treatment of military service members with moderate to severe acute pain resulting from combat injuries, further supporting prehospital trauma care guidelines currently in place for the battlefield.<sup>10</sup>

This is a study of data collected from the prehospital battlefield environment, predominantly during the conduct of tactical combat casualty care. Although data fields were complete on only 68.9% of patients, it should be noted that gathering such prehospital data under battlefield conditions has historically proven quite challenging.<sup>49,50</sup> While data for most were recorded at the time of treatment, some patient documentation was delayed by hours or days and sometimes weeks owing to the environmental and tactical constraints of combat operations.

## CONCLUSION

The prehospital medical providers depicted in this study were well trained, and many had years of combat experience from which to formulate clinical judgments for using OTFC on the battlefield. Battlefield pain management remains a priority for the US military's combat casualty care research program as ongoing improvements in battlefield pain management include refinements in education and training for medical personnel throughout the US military. Acute pain management in the prehospital environment will remain an area of focus as early pain control is more than just short-term symptom resolution—it is also an influence on long-term health and well-being.

Documentation, data capture, and research on prehospital battlefield treatments can prove challenging. Most medical providers in this setting are often focused on providing lifesaving medical care while maintaining situational awareness and responsiveness to environmental considerations as well as an opposing military force. Although this is a retrospective study, with inherent limitations and limited follow-up data from higher echelons of care, administration of OTFC in the prehospital battlefield environment readily seems to be both safe and effective.

OTFC is a rapid and noninvasive pain management strategy that should be expanded for use throughout the military in the prehospital setting. OTFC has considerable implications for use in civilian prehospital and austere environments that should also be further explored. Prehospital use of OTFC for acute pain is both feasible and practical.

## AUTHORSHIP

I.S.W., R.S.K., and J.G.M. were responsible for the study conception, design, and supervision; I.S.W., R.S.K., J.G.M., A.P., and T.S.T. were responsible for the acquisition of data. R.S.K., M.F., and L.M. provided the analysis and interpretation of data; M.F. and L.M. provided administrative and technical support; I.S.W., R.S.K., and J.G.M. drafted the article, and all authors contributed substantially to its critical revision. I.S.W. and R.S.K. take responsibility for the paper as a whole.

## ACKNOWLEDGMENTS

We acknowledge the sacrifices of the casualties depicted in this article, as well as the Special Operations combat medics and Special Forces medical sergeants who provided care to them. We are also indebted to Paul Linskens and the staff at SOCMSSC for their assistance with data collection.

## DISCLOSURE

The authors declare no conflicts of interest.

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